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Induction Toxicity of a Modified Memorial Sloan-Kettering-New York II Protocol in Children With Relapsed Acute Lymphoblastic Leukemia: A Single Institution Study

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Although the chance of cure for children with acute lymphoblastic leukaemia (ALL) is high, their outlook with subsequent relapse is poor. Bone marrow transplantation may be an option for some, but the need for intensive reinduction chemotherapy regimens remains the best hope for effecting cure in the majority of relapsed children. The authors report the experience of using an intensive chemotherapy protocol (Memorial Sloan-Kettering-New York II Protocol, MSK-NY-II) in a series of relapsed children with ALL. Thirty children presenting to the Royal Alexandra Hospital for Children, Sydney, in their first relapse of ALL were treated according to a modification of the original MSK-NY-II protocol. Three children (10%) died during induction therapy, two from overwhelming Gram-negative sepsis, and one from intracerebral haemorrhage. Of 27 children completing induction, two children failed to enter remission; however, both had planned deviations from the protocol. Infectious complications were prominent with a total of 55 admissions for febrile neutropenic episodes. Eight children required the support of the intensive care unit for infectious complications. A total of 36 microbiological isolates were obtained from the patients during induction therapy. Ten bone marrow transplant procedures have been subsequently performed in these children, of whom five are alive and disease free at the time of writing. The MSK-NY-II protocol is an intensive regimen but with encouraging early remission rates in relapsed childhood ALL. Early sepsis in previously immunosuppressed children is an important cause of induction death.

Key words: chemotherapy, induction toxicity, relapsed leukemia

INTRODUCTION

With improvements in the therapy for children with acute lymphoblastic leukemia (ALL), the expected long-term continuous complete remission rate is presently in the region of 70% [1,2]. In the past, the outlook for relapsed patients has been poor [3–5]. With continuing experience in the use of multiagent chemotherapy, improvements in the supportive care of children with cancer, and the contribution of large multicenter studies such as those of the POG and BFM groups, the outlook for children with relapsed ALL showed improvement during the 1980s [6–10]. There are concerns that patients relapsing off current front-line therapies may demonstrate poorer prognosis due to the increased intensity of treatment they have received. It may therefore be necessary further to intensify chemotherapy protocols for relapsed patients.

One of the reasons for the improved continuous complete remission rates in childhood ALL is the use of intensive chemotherapy regimens in newly diagnosed patients recognised as being at high risk of relapse. One such therapy, the Memorial Sloan-Kettering-New York-II (MSK-NY-II) Protocol [11], has been recently reported. We report here our results using this protocol for the treatment of 30 children presenting with their first relapse of ALL.

MATERIALS AND METHODS

Patients

Patients attending the Oncology Unit of the Royal Alexandra Hospital for Children in first relapse of ALL were eligible for treatment. Between December 1989 and April 1994, 30 children were managed on a modified MSK-NY-II protocol. All patients had received initial treatment according to intensive, multiagent, contemporary protocols. Most children (n = 27) had been treated at original presentation with the Australian and New Zealand Children's Cancer Study Group (ANZ-CCSG)

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Study V protocol [12]. Two children had received individualised therapies and one child had been treated on the latest ANZ-CCSG Study VI protocol.

Memorial Sloan-Kettering-New York-II Protocol

Patients were treated according to a modified version of the regimen II-B arm of the Memorial Sloan-Kettering-New York-II protocol. Briefly, induction (outlined in Fig. 1) consisted of daunomycin 60 mg/m^2/d IV, days 1,2 by 48 hr continuous infusion. In a modification to the original protocol, most patients (20/30) received etoposide 250 mg/m^2/d IV, as a continuous 72 hr infusion in place of the initial daunomycin infusion. This was an attempt to prevent excessive cardiotoxicity in patients who had previously received anthracycline chemotherapy. The maximum previous exposure to anthracyclines for any patients was 200 mg/m^2. The decision to use etoposide during induction was made by the treating physician and was not based on a specific cutoff dose of prior anthracycline exposure. Other than this modification, the rest of induction/consolidation was exactly the same as described in the original MSK-NY-II protocol. Cyclophosphamide 1,200 mg/m^2 IV, followed on day 3: Vincristine 1.5 mg/m^2 IV, day 1, then weekly for four doses: Prednisolone 60 mg/m^2/day PO, days 1–29 (with a 7-day tapering dose): Asparaginase 6,000 U/m^2/day IM, starting day 4 for a total of nine doses on Monday, Wednesday, Friday: IT methotrexate days 1, 15, and 22; 6, 8, 10, or 12 mg for ages <1, 1–2, 2–3, and >3 yr, respectively.

Consolidation commenced at day 29 with cytarabine 3 gm/m^2/day IV, days 29, 30 and 36, 37: Methotrexate 150 mg/m^2 IV, days 32 and 39: Vincristine 1.5 mg/m^2 IV, days 40 and 47: Prednisolone 180 mg/m^2/day PO, days 40–46: Asparaginase 6,000 U/m^2 IM, continued three times weekly until a total of 24 doses had been administered during induction and consolidation. Patients with CNS involvement at relapse did not receive radiotherapy as part of their consolidation; neither was testicular irradiation given to the child with isolated testicular relapse.

Remission status was assessed at the end of the combined induction/consolidation phase at ~ day 57. Patients did not have bone marrow status routinely checked at the end of induction at day 29.

Maintenance chemotherapy commenced at the time of neutrophil (>1.0 × 10^9/l) and platelet (>100 × 10^9/l) recovery. IT methotrexate, day 0 (and days 7, 15, and 22 in first cycle of maintenance only): 6-Thioguanine (6-Mercaptopurine in the original MSK-NY-II protocol) 300 mg/m^2/day PO, days 0–3: Cyclophosphamide 1,200 mg/m^2 IV, day 4 (600 mg/m^2 in first maintenance cycle): Vincristine 1.5 mg/m^2 IV, days 11, 18, and 25: Prednisolone 180 mg/m^2/day PO, days 18–25: Asparaginase 6,000 U/m^2, days 11, 13, and 15: Methotrexate 150 mg/m^2 IV, day 25 (dose escalated by 50 mg/m^2/cycle until ANC<50 × 10^9/l or mucositis occurred): Daunomycin 20 mg/m^2 as 6 hr infusion, days 40, 41 (etoposide 100 mg/m^2/day if used in place of daunomycin in induction): Cytarabine 40 mg/m^2/dose 12 hrly IV or SC, days 42–44: 6-Thioguanine 35 mg/m^2/12 hrly PO, days 42–44. The total duration of maintenance was 2 years.

RESULTS

Patients

Thirty children with ALL experiencing their first relapse were treated according to a modified MSK-NY-II protocol. Patient characteristics at the time of their original diagnosis and at relapse are shown in Table I. Median age at relapse was 6.89 yr with a median time to relapse from first remission of 2.25 yr. Of the 21 off-treatment relapses, five occurred <6 months from the time of completing first remission therapy.

Response to Induction/Consolidation Therapy

Ten children received daunomycin and 20 etoposide during initial remission induction therapy. There were three (10%) induction deaths; two children died from fulminating Gram-negative sepsis, and the third child died from an intracerebral haemorrhage while concurrently being treated for Gram-negative septicemia. All induction deaths occurred within the first 4 weeks of initiating therapy (1 received etoposide during induction, 2 received daunomycin). Of 27 children completing induction/consolidation, two failed to achieve second remission, giving an induction failure rate of 7%. Both of these children had major deviations from the protocol. One child with Trisomy 21 received no high dose steroid and only the first HD cytosine/MTX (at reduced dose) because of previous problems with severe methotrexate mucositis. She received an allogeneic transplant at a time when she had a hypoplastic bone marrow containing 3% blasts, but relapsed and died shortly after transplant. The second patient received no asparaginase due to previous anaphylaxis. She subsequently underwent autologous bone marrow transplant in second remission and is currently alive and disease free 1.73 yr from relapse. There was one further minor protocol deviation in a child with severe sepsis following the second cytosine/MTX block in whom induction therapy was terminated at this point (patient remains in 2nd CR). Thus all children completing the full induction/consolidation therapy went into remission. In those patients where induction was completed, this phase of therapy took an average of 73 days (range 56–128 days) to completion. Eleven of 24 patients completing the full induction schedule did so within 1 week of the planned 63-day induction course.

Toxicity of Induction and Consolidation Phases

Admissions for neutropenic fever and the need for intensive care unit (ICU) support are outlined in Table

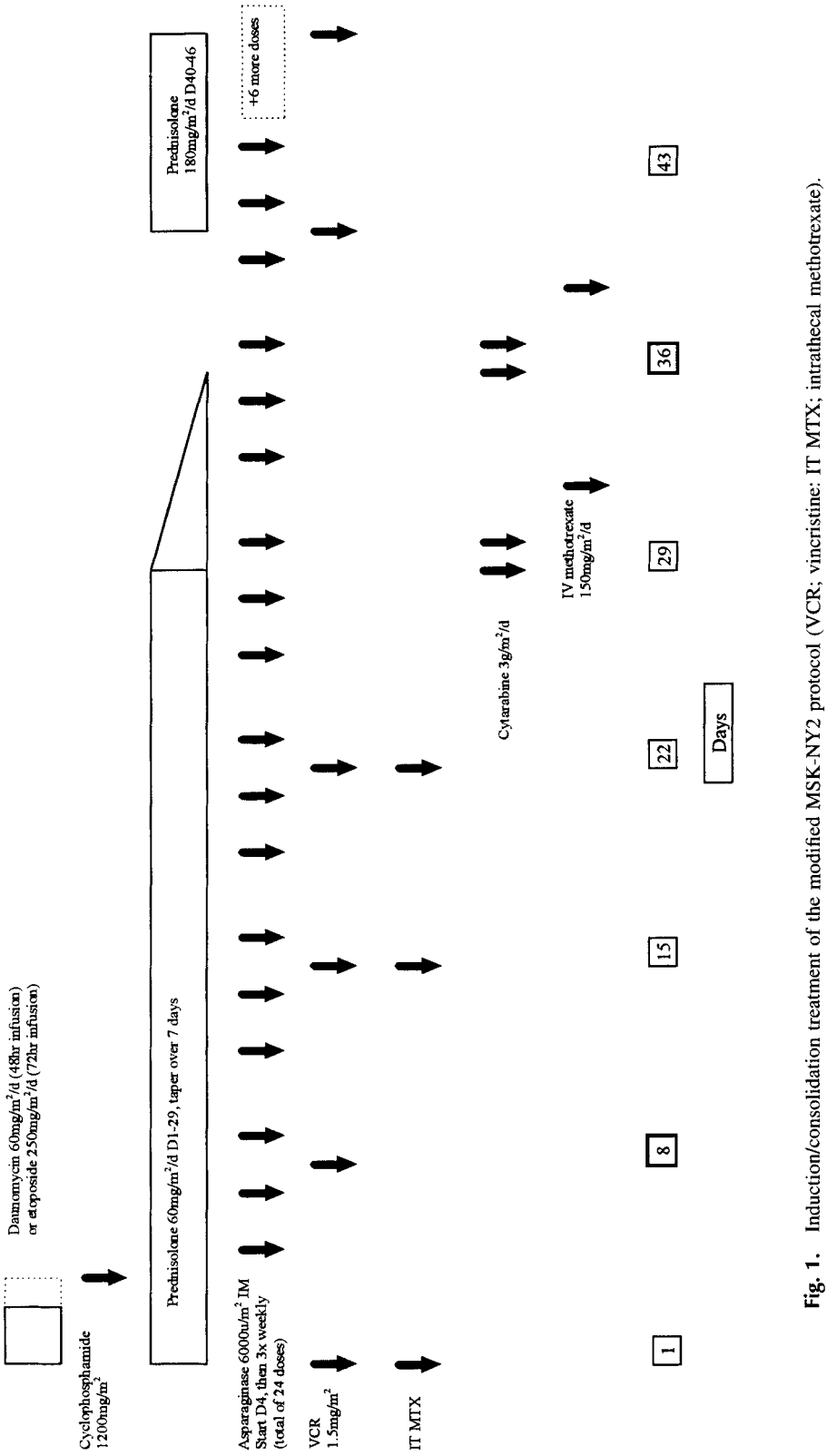

Fig. 1. Induction/consolidation treatment of the modified MSK-NY2 protocol (VCR; vincristine: IT MTX; intrathecal methotrexate).

TABLE I. Patient Characteristics

Total patients (n = 30)	Male (n = 18), female (n = 12)
Site of relapse	Bone marrow (n = 20)
	CNS (n = 6)
	Bone marrow and CNS (n = 3)
	Testicular (n = 1)
Relapse on or off treatment	Off (n = 21)
	On (n = 9)
Median length of 1st remission (yr)	2.25 (0.79–5.15)
Immunophenotype (n = 25)	Pre-B (n = 23) (CALLA +ve n = 21)
	Null cell (n = 1)
	T cell (n = 1)
Median age (yr)	Diagnosis 4.32 (1.75–15.66)
	Relapse 6.89 (3.13–19.1)
Median white blood cell count ($\times 10^9$/l)	Diagnosis 9.8 (0.8–420)
	Relapse 6.7 (1.0–27.4)

TABLE II. Admissions to Hospital for Neutropenic Fever During First 9 Weeks of Therapy

	Induction (days 1–29)	Post-1st HD cytarabine/MTX[a] (days 29–36)	Post-2nd HD cytarabine/MTX (day 35+)
Total admissions (n = 55)	27 (49%)	2 (4%)	26 (47%)
Total bed days (n = 823)	343 (42%)	59 (7%)	421 (51%)
Total ICU admissions (n = 8)	3 (38%)	0	5 (62%)
ICU bed days (n = 45)	5 (11%)	0	40 (89%)
Reason for ICU admission	Overwhelming gram-negative sepsis (n = 3)		ARDS[b]/Strep. mitis sepsis (n = 1) Encephalopathy with Staph./Strep. sepsis (n = 1) Klebsiella septicaemia/septic shock (n = 1) Septic shock/renal failure (n = 1) Protracted seizures (n = 1)

[a]High dose cytarabine and methotrexate.
[b]Adult respiratory distress syndrome.

II. A total of 55 hospital admissions for neutropenic fever occurred during the induction/consolidation phase of therapy. This accounted for 823 patient bed days. Thus on average, patients had two admissions, with a total of 27 bed days; 27 admissions (49%) occurred during the first 4 weeks of induction, 26 (47%) after the second high dose Cytosine/MTX block of consolidation therapy, and only 2 (4%) between the first and second HD Cytosine/MTX consolidation blocks. There were 45/823 (5%) patient bed days in ICU during the total induction/consolidation phase and no significant difference between deaths during induction, total admissions, and bed days for febrile neutropenia between the patients receiving daunomycin or etoposide.

The microbiological isolates during induction/consolidation are outlined in Table III. Of the early induction admissions for neutropenic fever, there were 21 microbiological isolates in 23 patients. Eight patients had no microbiological evidence of infection, and five patients had two or more different isolates. All of the induction deaths occurred during this phase of treatment; however of the total of 45 ICU bed days during induction/consolidation, this first 4 weeks of therapy accounted for only 5 ICU bed days (11% of total ICU bed days).

Twenty-six admissions for febrile neutropenia occurred after the second consolidation dose of HD cytosine/MTX and accounted for 51% of the total bed occupancy during induction/consolidation. There were no infective deaths during this period; however, five children required ICU support for an average of 8 days each and were responsible for 89% of the total ICU admissions. Twenty microbiological isolates were obtained from 15 patients (Table III). There were two significant neurological events following this phase of therapy. One patient had prolonged and protracted seizures requiring ICU support; a second child developed a severe peripheral neuropathy. There were only two admissions following the first HD cytosine/MTX block, one child with *Escherichia coli* septicaemia and a second child with pyrexia of unknown origin. Neutrophil recovery to an ANC of 0.5×10^9/l took an average of 22 days (range 16–49 days) from the start of induction; platelet recovery to 50×10^9/l took an average of 18 days (range 11–49 days).

Outcome

There have been a total of 11 deaths (induction n = 3, BMT-related n = 3, disease-related following subsequent relapse n = 5). Another child has relapsed and is currently

TABLE III. Episodes of Febrile Neutropenia During Induction/ Consolidation Associated with Microbiologically Documented Pathogens

Pathogen isolated	Number of febrile episodes associated with positive cultures: Induction (days 1–29)	Consolidation (days 30–57)
E. coli	9	9
Streptococcus species	6	6
Staphylococcus species	1	1
Klebsiella sp.	1	2
Candida albicans	1	1
H. influenzae	1	
Respiratory syncitial virus	1	
Herpes simplex	1	
Pseudomonas sp.		1

in third CR following salvage therapy. Data is as yet too immature to provide meaningful survival curves.

A total of 10 BMT procedures have been undertaken in these children (1 autologous, 8 allogeneic, 1 MUD). The decision to transplant patients was determined by the treating physician, but where a suitable family donor was identified the recommendation was to transplant in 2nd remission. The autologous transplant was performed in a 5-year-old boy with combined BM and CNS relapse <6 months from completion of first remission therapy in whom no family donor was available. The MUD transplant was in an 8-year-old boy with an off therapy bone marrow relapse who had a high white cell count (420×10^9/l) at first presentation. Three children died from complications following BMT. There have been two deaths following subsequent relapses 5 and 8 months after BMT. Five children remain in second CR following BMT 0.95–2.04 yr from time of relapse.

DISCUSSION

We have described the use of an intensive chemotherapy regimen in 30 children with relapsed ALL. Although originally designed for the management of high risk children at diagnosis, we have been able to demonstrate its efficacy in relapsed patients. As this is an aggressive protocol, we have concentrated on documenting toxicity during induction, an area that many other studies report in little detail or not at all. There is a developing body of evidence to suggest that such treatment is necessary for long-term cure for relapsed ALL [13]. The number of induction deaths (10%) may be regarded as high; however, all of these deaths occurred during the initial induction phase. This reinduction phase is no more dose intensive than many other relapse protocols, and therefore we feel that although the MSK-NY-II protocol is dose intensive at later stages of therapy, this cannot account for the number of early deaths. In addition, the original description of the MSK-NY-II protocol described a total of four deaths in 44 patients during the same period of treatment and this in previously untreated patients. In newly diagnosed ALL patients treated at the Royal Alexandra Hospital for Children, there has been one induction death in 133 patients over the same time period as this study. Clearly, the pattern of induction death among relapsed and newly diagnosed patients will be different. There are likely to be less adverse metabolic events in relapsed patients who rarely have massively elevated white cell counts or bulky disease at the time of relapse since they are usually being routinely followed up in clinic. This is borne out by the fact that in this study, whereas six patients had WBC $>50 \times 10^9$/l at original presentation, there were no relapsed patients with this level of WBC elevation.

Infection is the major risk for this group of patients and may be related to the immunosuppression induced by therapy in first remission. It is interesting to note that whereas all of the deaths occurred within the first 4 weeks of initiating treatment and these patients accounted for the three ICU admissions during this time, they died very quickly (only 5 bed days). We are aware of delays in obtaining appropriate management and antimicrobial therapy in two of these children. This is a protocol that demands close patient observation and the use of intensive resources, with each patient requiring an average of two admissions lasting 13 days each during the 9-week induction phase. Each child required at least one admission for a febrile neutropenic event.

The two periods when patients were most likely to develop significant infection were in the first 4 weeks of induction therapy and following the neutropenia induced by the Cytosine/MTX blocks. The median duration of hospitalisation during the first 4 weeks of therapy for fever-related illness was 14 days. This compares to the 26 days admission reported in the original MSK-NY-II report. There are a number of explanations for this, including the admission/discharge policy for the individual units, the need for newly diagnosed patients and families to spend longer learning about the disease, and the higher incidence of complications such as tumour lysis in newly diagnosed patients. The median duration of admission in the latter half of induction was similar between this study and the original MSK-NY-II report (12 vs. 13 days). The incidence of significant (microbiologically proven) infection was higher in our relapsed group of patients compared to the original MSK-NY-II patients (31 episodes in 30 patients vs. 31 episodes in 44 patients). Again, the interpretation of this is difficult and depends on a number of variable factors and cannot be explained solely by the fact that relapsed patients are more likely to develop infection due to prolonged immunosuppression.

It is interesting to note that we experienced a lot of infective toxicity following the second cytosine/MTX consolidation treatment (51% of all admissions, 89% of ITU admissions), although there were no deaths during

this phase of treatment. The original MSK-NY-II protocol was amended for the last six patients who received just one cytosine/MTX block because of concerns with toxicity. It should be borne in mind, however, that the majority of our patients were treated with the original MSK-NY-II protocol before its publication and subsequent amendments. In light of the results presented in our study, we feel that a similar reduction in consolidation treatment also should be recommended for relapsed patients. We have no evidence to suggest this level of consolidation therapy is likely to be less or more effective. One further approach to the reduction in infectious complications may be the use of cytokine (Granulocyte-colony stimulating factor) support [17]. We have used G-CSF support during febrile neutropenic admissions in six children recently started on the modified MSK-NY-II protocol in the hope that it may reduce the severity of potentially life-threatening infectious complications in these children. To date, however, we have insufficient data to confirm this belief.

Clearly, with relapse-free survival rates on the order of 70–80% for children in first remission following treatment for ALL, the challenge is to provide effective therapy for those children who suffer subsequent relapse. A number of studies of relapsed ALL have published data reporting remission rates on the order of 90–100%, and disease-free survival on the order of 30–40% [8,10,14–16]. Whereas the remission rate in this study compares favourably with these previously published results, our data are as yet too immature to make the comparisons for disease-free survival. In addition, it could argued that since remission status was checked after a prolonged and intensive induction phase of 9 weeks, we may be reporting a higher remission induction rate than if we had looked at bone marrow status after 4 weeks therapy when most of the other reported studies would be performing remission analysis.

In conclusion, we present the data collected on a series of 30 patients treated in their first relapse of ALL using a modification of the MSK-NY-II protocol. The protocol is dose intensive with a high induction remission rate. Toxicity, especially infectious complications, are significant, and some patients need considerable intensive supportive care. Although our data are as yet relatively immature to provide long-term survival figures, we feel that pushing the extremes for those children in whom allogeneic bone marrow transplantation is not an option. We continue to treat all patients in their first relapse of ALL at any site on the modified MSK-NY-II protocol.

REFERENCES

1. Rivera GK, Raimondi SC, Hancock ML, Behm FG, Pui CH, Abromowitch M, Mirro J, Ochs JS, Look AT, Williams DL, Murphy SB, Dahl GV, Kalwinsky DK, Evans WE, Kun LE, Simone JV, Crist WM: Improved outcome in childhood acute lymphoblastic leukemia with reinforced early treatment and rotational combination chemotherapy. Lancet 337:61–66, 1991.
2. Chessells JM, Bailey CC, Richards S. MRC UKALL X: The UK protocol for childhood ALL: 1985–1990: The Medical Research Council Working Party on Childhood Leukaemia. Leukemia 6 Suppl. 2:157–161, 1992.
3. Rivera G, Murphy SB, Aur RJA, Verzosa MS, Dahl G, Mauer AM. Recurrent childhood lymphocytic leukemia. Cancer 42:2521–2528, 1978.
4. Chessells JM, Cornbleet M. Combination chemotherapy for bone marrow relapse in childhood lymphoblastic leukaemia. Med Pediatr Oncol 6:359–365, 1979.
5. Ekert H, Ellis WM, Waters KD, Matthews RN. Poor outlook for childhood acute lymphoblastic leukaemia. Med J Aust 2:224–226, 1979.
6. Buchanan GR, Rivera GK, Boyett JM, Chauvenet AR, Crist WM, Vietti TJ. Reinduction therapy in 297 children with acute lymphoblastic leukemia in first bone marrow relapse: A Pediatric Oncology Group Study. Blood 72:1286–1292, 1988.
7. Culbert SJ, Shuster JJ, Land VJ, Wharam MD, Thomas PRM, Nitschke R, Pinkel D, Vietti TJ: Remission induction and continuation therapy in children with their first relapse of acute lymphoid leukemia. Cancer 67:37–42, 1991.
8. Sadowitz PD, Smith SD, Shuster J, Wharam MD, Buchanan GR, Rivera GK: Treatment of late bone marrow relapse in children with acute lymphoblastic leukemia: A Pediatric Oncology Group Study. Blood 81:602–609, 1993.
9. Henze G, Fengler R, Buchmann S: Erste Ergebnisse einer Studie zur Behandlung von Kindern mit ALL-Rezidiven. Onkologie 9:92–95, 1986.
10. Henze G, Fengler R, Hartmann R, Kornhuber B, Janka-Schaub G, Niethammer D, Riehm H: Six-year experience with a comprehensive approach to the treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85): A relapse study of the BFM Group. Blood 78:1166–1172, 1991.
11. Steinherz PG, Redner A, Steinherz L, Meyers P, Tan C, Heller G: Development of a new intensive therapy for acute lymphoblastic leukaemia in children at increased risk of early relapse: The Memorial Sloan-Kettering-New York-II protocol. Cancer 72:3120–3130, 1993.
12. Waters KD: A randomised clinical trial of modified BFM therapy versus modified high dose asparaginase therapy in childhood acute lymphoblastic leukaemia by the Australian and New Zealand Children's Cancer Study Group. Med Pediatr Oncol 20:391, 1992.
13. Chessells JM, Lieper AD, Richards SM: A second course of treatment for childhood acute lymphoblastic leukaemia: long-term follow-up is needed to assess results. Br J Haematol 86:48–54, 1994.
14. Rivera G, George SL, Bowman WP, Kalwinsky D, Ochs J, Dahl GV, Hustu HO, Simone JV: Second central nervous system prophylaxis in children with acute lymphoblastic leukemia who relapse after elective cessation of therapy. J Clin Oncol 1:471–476, 1983.
15. Pui C-H, Bowman WP, Ochs J, Dodge RK, Rivera GK: Cyclic combination chemotherapy for acute lymphoblastic leukemia recurring after elective cessation of therapy. Med Pediatr Oncol 16:21–26, 1988.
16. Henze G, Fengler R, Niethammer D, Schellong G, Riehm H: BFM group treatment results in relapsed childhood acute lymphoblastic leukemia. Haematol Bluttransfus 33:619–626, 1990.
17. Mempel K, Reiter A, Yakisan E, Odenwald E, Pfetsch M, Welte K, Schwab G, Riehm H: A randomised phase III study of recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF) in childhood high risk acute lymphoblastic leukemia. Blood 82 Suppl. 1:194a, 1993.